REMARKS

Applicant has amended claims 72, 75-77, 82-83, and 104-108. The new term "plasmid" is supported at least at page 34, lines 28-30, and the new term "autologous" is supported at least at page 38, lines 1-9. Claims 72-78, 82-84, and 104-108 are pending.

Interview Summary

Applicant thanks Examiners Crouch and Woodward for the courtesy of the personal Interview of January 28, 2006, summarized on the Interview Summary (Form PTOL-413). Applicant will discuss the Interview below in the context of the pending rejections.

Interference Estoppel Rejection

The Examiner rejected claims 72-78, 82-84, and 104-108 over the count from Interference No. 104,714 (Selden v. Morgan) because Applicant requested adverse judgment. [Office Action at p. 2.] Applicant respectfully traverses the rejection.

As Applicant explained during the interview, the count concerns the genus of *ex vivo* gene therapy, while Applicant's claims are directed to the species of non-viral *ex vivo* gene therapy. Applicant has submitted numerous references showing that the art taught away from non-viral gene therapy, and Applicant has overcome several prior art rejections by relying upon those references to show that non-viral *ex vivo* gene therapy is a separately patentable species of the genus of *ex vivo* gene therapy.

Examiner Crouch indicated during the interview that she agreed that non-viral *ex vivo* gene therapy is a separately patentable species and requested that Applicant merely refer to where those arguments and papers are already of record. Applicant first submitted such evidence to overcome prior art rejections in the Amendment of March 11, 1998 [pp. 40-46] and has referred to that evidence several times since. [*E.g.*, Amendment of October 5, 1999 at pp. 21-31.]

The separate patentability argument would rebut any rejection of the claims under 35 U.S.C. §§ 102(g) or (f) over the count, although the Examiner did not expressly make any such

rejection. Rather, the Examiner expressly rejected the claims over the count on the ground of interference estoppel, relying upon 37 C.F.R. § 1.658(c).[1]

Even if the species claims were separately patentable from the generic count, interference estoppel would exist if Applicant could have moved in interference 104,714 to have the species subject matter (non-viral gene therapy), added to the interference, or to have a new interference declared on that subject matter. As discussed with Examiner Woodward during the interview, however, Applicant could not have made any such motion because Morgan had no disclosure of non-viral *ex vivo* gene therapy to support such a claim and count. Because that subject matter was not common to both applications, there was no basis for Applicant to move in the interference to have that subject matter contested. Thus, there is no interference estoppel for non-viral *ex vivo* gene therapy.

As discussed during the interview, the MPEP even has an example directly on point in § 2363.03.[2] Example 8 involves an Applicant AT who discloses the genus "solvent" and the species "benzene" and claims the genus "solvent". Applicant AU similarly discloses the genus "solvent" and the species "benzene" and claims the genus "solvent", but AU also discloses the species "toluene." An interference is declared on the generic count "solvent," and judgment is entered in favor of AT. Nonetheless, AU would not be estopped to obtain a claim to "toluene" if "'toluene' defines a 'separate patentable invention' from 'solvent.'" The following chart illustrates this, with the bolded species being those not subject to interference estoppel if they are a separate patentable invention from the generic count:

Applicant	disclosed genus/count	disclosed species 1	disclosed species 2
AT	solvent	benzene	
Morgan	*ex vivo* gene therapy	viral	
AU	solvent	benzene	**toluene**
Selden	*ex vivo* gene therapy		**non-viral**

[1] Applicant notes that this rule was superseded by 37 C.F.R. § 41.127(a)(1). *See* 69 Fed. Reg. 49960 (August 12, 2004). However, that section "recodifies the existing estoppel provision for interferences." 69 Fed. Reg at 49968. col. 1.

[2] Applicant notes that the PTO recently revised the interference chapter of the MPEP, and this specific example is no longer present. However, Example 3 of § 2308.03 illustrates in more general terms that interference estoppel does not apply in such a situation unless the Examiner demonstrates that the species would have been obvious in light of the genus.

Because non-viral *ex vivo* gene therapy is a separate patentable invention from *ex vivo* gene therapy, and the Morgan application did not disclose non-viral *ex vivo* gene therapy, there is no interference estoppel.

The Board's formulation of interference estoppel agrees with this example that interference estoppel cannot exist for separately patentable subject matter that is not common to the parties' disclosures:

> We agree with Nelson that the doctrine of interference estoppel holds that an interference settles not only the rights of the parties under the issues or counts of the interferences but also settles every question as to the rights to **any claim which might have been presented or determined** in the interference proceeding. *In re Risse*, 378 F.2d 948, 154 USPQ 1 (CCPA 1967). The basis or purpose of the doctrine of interference estoppel is to insure the resolution of priority in a single contest respecting **all common subject matter** disclosed by the parties. *Stoudt v. Guggenheim*, 651 F.2d 760, 210 USPQ 359 (CCPA 1981).

Nelson v. Bowler, 1 USPQ2d 2076, 2079 (Bd. Pat. App. & Int. 1986)(emphasis added).

The PTO's reviewing court's formulation of interference estoppel also agrees:

> [A]n interference settles not only the rights of the parties under the issues or counts of the interference but also settles every question of the rights to **any claim which might have been presented and determined in the interference proceeding**. *In re Chase*, 71 F.2d 178, 21 CCPA 1183; *Avery v. Chase*, 101 F.2d 205, 26 CCPA 823; In *re Gregg*, 244 F.2d 316, 44 CCPA 904, and cases cited therein. While the doctrine of estoppel has been applied where a party has neglected or refused to contest priority of patentable **subject matter which is clearly common to his application and the application of his opponent** in interference (see *In re Long*, 83 F.2d 458, 23 CCPA 1078, and *In re Rhodes*, 80 F.2d 525, 23 CCPA 816), we can express no opinion on that issue where it is not certain the board intended to raise it, and where it is not clear from the board's opinion whether it regarded the Ullyot patent specification, when considered as a whole, to **clearly disclose** the chemical compounds recited in appealed *1675 claims 12, 13 and 18 (*In re Rhodes, supra*; *Lawson v. Bruce*, 222 F.2d 273, 42 CCPA 893; *Binstead v. Littmann*, 242 F.2d 766, 44 CCPA 839; 113 USPQ 279; *Mahan v. Doumani*, 333 F.2d 896, 51 CCPA 1516).

In re Yale, 146 USPQ 400 (CCPA 1965)(emphasis added).

Because Morgan's application does not support non-viral gene therapy, Applicant could not have moved in the interference to contest that subject matter, and interference estoppel does not apply to that separately patentable subject matter.

While the MPEP used to require the involvement of an APJ before a losing party's application could be allowed, MPEP §. 2363.03 at p. 2300-36 (August 2001), Applicant notes that recent revision now only discusses the involvement of an Interference Practice Specialist. MPEP § 2308.03 at p. 2300-23 (October 2005). Accordingly, Applicant respectfully requests timely withdrawal of this rejection.

Written Description Rejection

The Examiner rejected claims 72-78, 82-84, and 104-108 under 35 U.S.C. § 112, first paragraph, as allegedly not being supported by an adequate written description for the recitations concerning "endogeneous retroviral sequences" and "chronic viral infection." [Office Action at p. 3.] As discussed during the interview, however, the Examiner is not reinstating previous rejections relating to the alleged lack of disclosure of non-viral *ex vivo* gene therapy. Rather, the Examiner does not believe the application supports the specifically quoted language. Indeed, the Examiner proposed amending the claims to recite "plasmid." Applicants have amended the claims as the Examiner suggested, deleting the language of concern and adding "plasmid." Accordingly, this rejection is moot.

Enablement Rejection

The Examiner rejected claims 72-78, 82-84, and 104-108 under 35 U.S.C. § 112, first paragraph, as allegedly not being enabled on several grounds. [Office Action at p. 4.] As Applicant shows below, none of these grounds supports the enablement rejection. Indeed, Applicant's invention has been recognized as pioneering, has been used by others with other genes and other cells, achieved a therapeutic effect in an animal model, and even achieved a therapeutic effect in humans.

The Decision in Interference No. 104,712 does not support the rejection

The Examiner asserted that the Board found in Interference No. 104,712 (Anderson v. Morgan), that *ex vivo* gene therapy was not enabled except for a narrow scope to one party. [Office Action at p. 5.] As discussed during the interview, the Decision in Interference No. 104,712 shows that the Board did not reach that conclusion. While only claims 5, 7, and 12 of

the Anderson patent's 14 claims survived the interference [Judgment at p. 2 (copy attached); *see also* Erratum (copy attached)], the Board found the other claims invalid for obviousness, not for lack of enablement. [Memorandum Opinion and Order (copy attached) at p. 5 (summarizing Morgan Preliminary Motions 1 and 2) and p. 55 (granting Morgan Preliminary Motions 1 and 2).] The references the Board relied upon are not available as prior art against Selden.

The Board found that Morgan's claims were invalid on enablement grounds. [Memorandum Opinion and Order at p. 4 (summarizing Anderson Preliminary Motion 1) and p. 55 (granting Anderson Preliminary Motion 1).] However, those grounds were specific to the Morgan application, which was fled two years before the Selden application. Specifically, Anderson argued that Morgan's claims required grafting a sheet of keratinocytes onto a patient, and that such a method had several problems. [Memorandum Opinion and Order at pp. 12-13.] In addition, Anderson relied upon later statements by the Morgan inventors indicating that their (viral) technique had not yet been successful. [Memorandum Opinion and Order at pp. 15-17.] In response to those arguments, the Board found Morgan's claims not enabled. Accordingly, the Board did not find *ex vivo* gene therapy to be enabled for only a narrow scope, and this ground does not support the rejection.

The Examiner also relied upon four references as allegedly indicating that the claimed invention is not enabled. [Office Action at pp. 5-6.] The very first of these (Lindahl), however, actually supports the enablement of the claimed invention. Applicant cannot find in the Lindahl article the passages the examiner attributes to it. Indeed, the Lindahl article favorably discusses Applicant's invention. As Applicant previously discussed [Amendment of March 11, 1998, at p. 19], the examples contained in the present application were reported in articles published in 1987 in *Science* [Selden et al., 236 *Science* 714-718 (1987)] and the *New England Journal of Medicine* [Selden et al., 317 *N. Eng. J. Med.* 1067-1076 (1987)]. The Lindahl article cites these articles as references 44 and 4, respectively. [Lindahl at pp. 389, 390.]

The Lindahl article cites the *New England Journal of Medicine* article to support its statement that cells that grow well in culture "may not require retroviral vectors; less efficient techniques could be employed for introducing genes, such as microinjection, electroporation or transfection using calcium phosphate." The less efficient techniques could be used because

cotransfection with a drug-resistance gene could be used to select the few transduced cells, which could be grown into a large population. [Lindahl at p. 385.]

Moreover, the Lindahl article states:

> Several genes have been introduced into fibroblasts and **have continued to be expressed** following implantation of the cells (Table 3). When mouse L cells were transfected with the human growth hormone gene and implanted intrperitoneally, **a physiological level of hGH was detected in the bloodstream**. The cells used were not autologous and were rejected after a short period, but immunosuppression improved implant survival so that hGH serum levels were detectable over a 14 week period (44).

[Lindahl at p. 387 (emphasis added).]

Thus, rather than support the enablement rejection, the Lindahl articles actually demonstrates the enablement of the claimed invention by indicating that Applicant expressed physiological levels of hGH.

The remaining articles the Examiner cites (Mulligan, Greenhalgh, and Ghazizadeh) do not support the enablement rejection because none of them discuss Applicant's invention. Indeed, they all focus on viral gene therapy. Thus, the Examiner's discussion of the Greenhalgh article concerns "retroviral transduction" and "other viruses such as AAV" [Office Action at p. 5, lines 18-22], and the Examiner's discussion of the Ghazizadeh article, which is entitled "**Virus-**Mediated Gene Transfer for Cutaneous Gene Therapy," concerns the use of "the retrovirus promoter." [Office Action at p. 5, lines 22-26.]

<u>Applicant's invention has been recognized as pioneering</u>

In contrast to the articles the Examiner relies upon, several other articles cite Applicant's work and recognize its novel and pioneering nature. Kawakami et al. recognized Applicant's work as pioneering in the field of somatic gene therapy:

> Somatic gene therapy has been performed in an animal model of diabetes and also has been used as a growth hormone-supplying system in mice (2-4,5). These efforts **pioneered the field** of somatic gene therapy for hormone deficiency by **proving that even a few fibroblasts and keratinocytes can supply enough hormone to these animal models**.

[Kawakami et al., 41 *Diabetes* 956-961 (1992)(copy attached) at p. 956 (emphasis added).] Reference "2" is Applicant's 1987 *Science* article, and reference "4" is the 1987 *New England Journal of Medicine* article.

Simpson et al. also paid tribute to the pioneering nature of Applicant's work:

> Experiments with mice bearing an intact human insulin gene inserted into mouse Ltk-fibroblast cells **pioneered the field** of somatic gene therapy in diabetes by **proving that transfected fibroblasts can supply enough insulin in diabetic mice to normalize their blood glucose.**[2]

[Simpson, 2 *Gene Therapy* 223-231 (1995)(copy attached) at p. 223 (emphasis added).] Footnote "2" is Applicant's 1987 *New England Journal Of Medicine* article.

Similarly, Lauffenburger et al. referred to Applicant's transkaryotic implantation method as a "primary example" of a method for transporting growth factors through cellular matrices. [Lauffenburger et al., 52 *Biotechnology and Bioengineering* 61-80 (1996)(copy attached) at p. 71, col. 1).]

Applicant's invention has been used with numerous genes and cell types

Besides these articles specifically extolling the virtues of the Applicant's invention, numerous scientists have expanded upon Applicant's work to express numerous genes in numerous cells *in vivo.*

The Simpson et al. article discussed above expressed insulin in hepatocytes and achieved insulin synthesis, storage, and acute insulin release. [Simpson et al. at abstract.]

Rosenberg et al. expressed nerve growth factor (NGF) in fibroblasts *in vivo* and found the NGF prevented in rats the degeneration of cholingeric neurons that would have otherwise died without treatment. [Rosenberg et al., 24 *Science* 1575-1578 (1988)(copy attached) at abstract.] Commenting on Applicant's *Science* article, Rosenberg et al. stated that their "present study . . . extends the feasibility of such an approach." [Rosenberg et al. at p. 1576.]

Tani et al. expressed human granulocyte colony-stimulating factor (G-CSF) in fibroblasts *in vivo* to supplement cytokine production by gene therapy. [Tani et al., 74 *Blood* 1274-1280 (1989)(copy attached).] The G-CSF expression in mice caused significant neutrophilia and an increase in hematopoietic progenitors. [Tani et al. at p. 1277, col. 2.] Applicant 's work is specifically acknowledged at page 1274, col. 1.

Ogura et al. expressed α-interferon in fibroblasts *in vivo* for antitumor therapy. [Ogura et al., 50 *Cancer Research*, Vol. 50, pp. 5102-5106 (1990)(copy attached).] The α-interferon therapy significantly suppressed tumor growth in mice *in vivo*. [Ogura et al. at abstract.] Once again, tribute is paid to Applicant's invantion. [Ogura et al. at 5102, col. 1.]

Teumer et al. expressed human growth hormone (hGH) in keratinocytes *in vivo* in athymic mice. [Teumer et al., 4 *FASEB J.* 3245-3250 (1990)(copy attached) at pp. 3245-46.] The expressed hGH was detected *in vivo* in mice at concentrations in the physiological range. [Teumer et al. at abstract.] Once again, the authors pay tribute to Applicant's technique. [Teumer et al. at 3245.]

Yanagita et al. expressed proinsulin in monkey kidney (COS-7) cells, CHO cells, and human hepatoma cells, in addition to fibroblasts. [Yanagita et al., 133 *Endocrinology* 639-644 (1993)(copy attached) at abstract.] The authors reported that they were "currently in the process" of extending this work with the possibility of using it for a hybrid artificial islet or for gene therapy, citing Applicant's 1987 *New England Journal of Medicine* article. (Yanagita et al., 133 *Endocrinology* 639-644 (1993) at p. 643, col. 2).

Zhou et al. expressed glutamic acid decarboxylase (GAD) in fibroblasts *in vivo*. [Zhou, et al. 2 *Cell Transplantation* 193-205 (1993)(copy attached) at abstract.] Applicant's work is also referred to in this article. [Zhou et al., footnotes 25 and 26.]

Rosenthal et al. expressed GM-CSF in fibroblasts *in vivo* [Rosenthal et al. 84 *Blood* 2960-2965 (1994)(copy attached) at abstract.] They obtained expression *in vivo* that accelerated neutorophil recovery in response to irradiation-induced neutropenia. [Rosenthal et al. at p. 2964, col. 2.] The authors reported that the application of G-CSF gene-transfected cells in gene therapy was "currently under investigation in our laboratory", citing Applicant's 1987 *Science* and *New England Journal of Medicine* articles.

Cao et al, expressed α-interferon in fibroblasts *in vivo* for anti-tumor therapy in mice. [Cao et al., 121 *J. Cancer Res. Clin. Oncol.* 457-462 (1995) (copy attached.] The α-interferon therapy inhibited tumor growth and extended the survival time for the mice. [Cao et al. at abstract.] Applicant's 1987 *Science* article is cited at page 458, column 1.

Moritani et al. expressed IL-10 in T helper cells *in vivo* in mice. [Moritani et al. 98 *J. Clin. Invest.* 1851-1859 (1996)(copy attached) at abstract.] The IL-10 suppressed induced

autoimmune diabetes in a non-obese diabetic (NOD) mouse model. [Moritani et al. at abstract.] They referred to Applicant's published work as part of "the starting basis" that afforded them the opportunity to develop their concept of somatic gene therapy. [Moritani et al. at pp. 1858, col. 2.]

Rohrer et al. expressed nerve growth factor (NGF) in adrenal cells *in vivo*. [Rohrer et al. 5 *Cell Transplantation* 57-68 (1996)(copy attached) at p. 58, col. 2.] Untransformed rat adrenal cells transplanted to rat brains did not differentiate and formed tumors, while the transformed rat adrenal cells, which expressed NGF, differentiated and were nontumorgenic. [Rohrer et al. at p. 65, col. 1.] Applicant's work is cited at page 57, column 1.

Rage et al. expressed transforming growth factor α (TGFα) in fibroblasts. [Rage et al., 94 PNAS 2735-2740 (1997)(copy attached) at abstract.] When the cells were implanted in immature rats, they accelerated sexual maturation. [Rage et al. at abstract.] Rage stated they "used the somatic cell gene therapy approach of transkaryotic implantation (10) for targeting TGFα overexpression near LHRH neurons." [Rage et al. at p. 2735, col. 2.] Reference 10 is Applicants 1987 *Science* article.

Cao et al. expressed IL-3 and IL-6 in fibroblasts in mice *in vivo*. [Cao et al., 76 *J. Mol. Med.* 782-789 (1998)(copy attached).] The therapy significantly increased the numbers of platelets, neotrophils, and total white blood cells in peripheral blood. [Cao et al. at abstract.] In a mouse model of hematopoietic depression for patients after chemotherapy, the expressed interleukins accelerated recovery of platelet, neutrophil, and white blood cell counts. [Cao et al. at abstract.] Applicant's 1987 *Science* article is cited at page 783, column 1.

These articles show that scientists have used Applicant's approach to express numerous genes in numerous cells *in vivo*.

The death of Applicant's mice does not undermine the invention's enablement

The Examiner also questioned the enablement of the claimed invention because the mice in the examples died from overexpression of the introduced gene. [Office Action at p. 6.] However, Applicant demonstrated control of expression of the introduced genein Example 5 in the application:

> As described above, the plasmid pXGH5 contains the mouse metallothionein-I promoter.
>
> * * *
>
> **Of substantial importance is the fact that the cells, once in place in the animal, could still be modulated by external means. This result strongly suggests that in a clinical setting the expression of a desired or effector gene product could be modulated of pharmacologic intervention.**

[Application at pp. 44-45 (emphasis added).]

Indeed, Applicant's control of expression has been recognized by other scientists. For example, Stewart et al. commented on Applicant's work as follows:

> We recently established a transformed cell line, AtT20MtIns-1.4, which releases human insulin (Stewart et al. 1993). In this line the human preproinsulin (hppl) gene is driven by a zinc-sensitive mouse metallothionein (mMt-I) promoter (Taylor et al. 1991, Taylor & Docherty 1992). Incubation of AtT20MtIns-1.4 cells with a raised concentration of zinc increased insulin release (Taylor et al. 1991, Stewart et al. 1993). This raised the possibility that changes in zinc consumption could provide a crude means of controlling expression of the hppl gene after the AtT20MtIns-1.4 cells have been implanted into a host animal. **Such a control mechanism has been demonstrated after implantation of transformed fibroblasts expressing an exogenous human growth hormone gene driven by the mMt-I promoter (Selden et al. 1987b).**

[Stewart. et al., 142 *J. Endocrinology* 339-343 (1994)(copy attached) at p. 339, col. 2.] "Selden et al. 1987b" is Applicant's 1987 *Science* article. Stewart et al. expressed insulin in pituitary cells.

Similarly, Asakuno et al. reported on Dr. Selden's control of expression as follows:

> Selden et al. have reported the control of a transfected gene in intraperitoneal transplantation using human growth hormone (hGH) under the control of the mouse metallothionein 1 promoter [15].

(Asakuno et al., 702 *Brain Research* 23-31 (1995) at p. 29, col. 1). Reference "15" is Applicant's 1987 *Science* article. Asakuno et al. expressed c-Fos in fibroblasts *in vivo*, resulting in cell growth and neovascularization.

Rage et al. used this very method to control the expression of TGFα in fibroblasts, citing Applicant's 1987 *Science* article. [Rage et al. at p. 2735, col. 1.] They reported that including the inducible mouse metallothionein-1 promoter "allows one to increase TGFα synthesis at will by means of heavy metal induction of the MT promoter." [Rage et al. at p. 2735, col. 2.]

Even if control of expression had not been demonstrated, the Selden application provides an enabling disclosure. Again, control of expression can be obtained by selection of the appropriate promoter, and the application contains several paragraphs teaching how to use various promoters to control expression *in vivo*. [Application at 18, line 28 to page 19, last line.] Accordingly, the death of the mice does not support the enablement rejection.

Applicant demonstrated a therapeutic effect in an accepted model of human disease

During the interview, the Examiner questioned whether Applicant had enabled nonviral *ex vivo* gene therapy because she was not aware that Applicant's invention had been used in a successful gene therapy.[3] Of course, that is not what enablement requires:

> There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders (see *In re Isaacs*, 347 F.2d 889, 146 USPQ 193 (CCPA 1963); *In re Langer*, 503 F.2d 1380, 183 USPQ 288 (CCPA 1974)), even with respect to situations where no art-recognized animal models existed for the human disease encompassed by the claims.

MPEP § 2107.03 IV. Rather, the enablement requirement can be satisfied by results in an accepted animal model of human disease. *In re Jolles*, 206 U.S.P.Q. 885, 890 (C.C.P.A. 1980). In *In re Brana*, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995), the Federal Circuit rejected the PTO's argument that *in vivo* tests in animals are merely preclinical tests and inaccurate predictions of the compound's effectiveness in treating the actual human body for enablement purposes. *Brana*, 34 U.S.P.Q.2d at 1442. The court pointed out the statutory requirements for a patent only require "statistically significant tests with 'standard experimental animals'." *Id.*; *see also In re Krimmel*, 130 U.S.P.Q. 215, 219 (C.C.P.A. 1961).

Applicant demonstrated just that. Example 10 modeled the treatment of diabetes by monitoring the effect of intraperitoneally injected Ltk+Ins cells on diabetic mice. To obtain

[3] Applicant strongly disagrees with the statement that the only utility the Application discloses is to obtain a therapeutic effect. [Office Action at p. 6.] The Examiner has not questioned the enablement of the other disclosed uses. [*E.g.*, Application at p. 15, lines 2-6.] "[I]f any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." MPEP § 2164.01(c). Accordingly, the rejection should be withdrawn on this ground. Because Applicant is submitting so much evidence of the enablement of the claimed invention for a therapeutic use, however, the Amendment focuses on that use.

chemically diabetic animals, C3H mice were treated with streptozotocin, and serum glucose levels were measured approximately 10 and 15 days later. Within one week post-implantation, a dramatic decline in serum glucose levels was noted in five of the mice (Figure 9, solid line). By two weeks post-implantation, normoglycemia was restored in these diabetic mice. The remaining five mice showed either a transient decline in serum glucose levels or no decline at all, suggesting that immunosuppression was not equally effective for every mouse. Control diabetic mice (Figure 9, dashed line) showed no reduction in serum glucose levels. Serum glucose levels continued to fall in the group of five responding animals. [Application at 52, lines 5-30.] The decline of serum glucose levels in five mice was the predicted therapeutic response to genetically engineered cells expressing the insulin gene, and, unequivocally, a therapeutic effect.

Streptozotocin-induced diabetes in the mouse had been used for a number of years before Applicant's demonstration of gene therapy. Like et al. described it as early as 1976. [Like et al., 193 *Science* 415 (1976)(copy attached).] Stearns et al. commented that "animals injected with the antibiotic streptozotocin (SZ) have an acute insulin deficit resembling that of individuals with insulin-dependent diabetes mellitus." [Stearns et al., 15 *Acta Anat.* 193-203 (1983)(copy attached) at p. 194, col. 1.]

In 1986, shortly before Applicant's work was published in *Science* and the *New England Journal of Medicine*, Schwab commented further on the streptozotocin diabetes model stating that: "Low dose streptozotocin-induced diabetes serves as a model of human-type I diabetes", referring to the Like and Rossini 1976 article. [Schwab et al. 12 *Immunopharmacology* 17-21 (1986) (copy attached) at p. 17, col. 1.]

Applicant's diabetes expert, Karl Geisen, M.D., had the following additional comments on the value and relevance of the streptozotocin-induced diabetes model in human diabetes therapy:

> The use of animals rather than humans in diabetes research has several advantages. Animal models provide an opportunity for investigating the effects of therapeutic agents developed for the prevention, treatment, or cure of diabetes and its complications before the therapeutics are administered to humans. Well-studied animal models have permitted experienced researchers to correlate between animal and human diabetes.

[Geisen Declaration (copy attached).]

A diabetes-like condition can be induced in rodents by pharmacologic intervention. More particularly, a well characterized model of Type I diabetes can be induced by administering the chemical agent streptozotocin to mammals, such as mice, rats, rabbits, dogs, and pigs. [Geisen Declaration at pp. 14-15.]

The destruction of β-cells and hyperglycemia are caused by streptozotocin treatment. The streptozotocin-treated mouse model has been known and used in the study of Type I diabetes for over 20 years. β-cell destruction is the primary defect in this streptozotocin model of diabetes disease. Normal blood glucose levels in the streptozotocin model can be restored by insulin treatment. Thus, use of the rodent model provides a means for studying experimental diabetes. [Geisen Declaration at pp. 16-18.]

It has been Dr. Geisen's experience that an insulin therapy that was found to be effective in the treatment of streptozotocin-induced diabetes in a mouse model would also exhibit effectiveness in the human. In Dr. Geisen's opinion, the insulin therapy, which Dr. Selden showed was effective in the streptozotocin-induced diabetic C3H mouse model, would be expected to be effective in humans. [Geisen Declaration at pp. 21-22.]

Dr. Geisen's opinion is based on his experience, which has included evaluating diabetes therapies in streptozotocin models of diabetes, the extension of these therapies to clinical trials in humans after effectiveness was shown in the streptozotocin model, and correlation of the results in the animal model with the results in humans for the same insulin therapy. It has been his experience that there is very high correlation between the results of a given insulin therapy in streptozotocin-induced diabetes in a mouse model and the results of the same insulin therapy in clinical trials in humans. [Geisen Declaration at pp. 23.]

Other scientists have recognized this therapeutic effect. According to Tani et al., "implantation of . . . genetically manipulated fibroblasts was shown to be effective in obtaining high serum levels of growth hormone, insulin, or α1-antitrypsin", citing Applicant's work. [Tani et al. at p. 1274, col. 1.] Kawakami et al. characterized Applicant's work as "proving that even a few fibroblasts . . . can supply enough hormone to . . . animal models." [Kawakami et al. at p. 956, col. 2.] Simpson et al. characterized Applicant's work as "proving that transfected fibroblasts can supply enough insulin in diabetic mice to normalize their blood glucose." [Simpson et al. at p. 223, col. 1.] Rosenthal et al. characterized Applicant's work as

demonstrating "therapeutic application of . . . cells in animal deficiency models." [Rosenthal et al. at p. 2960, col. 1.]

In summary, Applicant's use of the streptozotocin-induced model as a predictor of success in humans was consistent with the use of this model for a period of more than 10 years before publication of Applicant's pioneering gene therapy experiments. Scientists have recognized that Applicant's results with that model demonstrated a therapeutic effect in a animal model of a human disease.

<u>Applicant's invention has actually been used in successful gene therapy</u>

Finally, while the enablement requirement does not require demonstration of a therapeutic effect in humans, Applicant's invention has indeed achieved such an effect. As the MPEP notes, "if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility." MPEP § § 2107.03 IV. Applicant has not only initiated human clinical trials but has actually achieved a therapeutic effect in those trials. Thus, there can be no remaining doubt that Applicant enabled non-viral *ex vivo* gene therapy.

Applicant conducted a phase I trial of nonviral *ex vivo* gene therapy in humans with severe hemophilia. [Roth et al., 344 *New Eng. J. Med.* 1735-1742 (2001)(copy attached) at abstract.] Applicant used the method disclosed in his 1987 *Science* (reference 13) and *New England Journal of Medicine* (reference 14) articles to transfect autologous fibroblasts with the human factor VIII gene and referred to this method as "transkaryotic implantation"—the title of the present application. [Roth et al. at p. 1736, col. 1.] Four of the six patients demonstrated increased levels of factor VIII activity. [Roth et al. at abstract.] Moreover, the increased levels of factor VIII activity correlated with increases in clinical measurements, such as decreased frequency of spontaneous bleeding episodes and decreased use of exogenous factor VIII. [Roth et al. at p. 1740, col. 1.] These clinical changes lasted up to approximately 10 months. [Roth et al. at abstract.]

Applicant's successful nonviral *ex vivo* gene therapy has been recognized by other scientists. Just in the last year, Long et al. recognized Applicant's clinical success:

> Implantation of autologous fibroblasts transfected *ex vivo* with B-domain-deleted human FVIII-encoding plasmid **clinically improved** four of six hemophilic patients [4].

[Long et al, 7 *J. Gene Med.* 494-505 (2005)(copy attached) at p. 495, col. 1 (emphasis added).] Reference 4 is the Roth et al. article. [Long et al. at p. 504, col. 2.]

Similarly, Chen et al. also recently recognized Applicant's clinical success:

> The strategy of achieving metabolic correction by *ex vivo* electroporation of somatic cells with a plasmid vector followed by *in vivo* implantation **has been shown to be clinically effective** in another metabolic disorder, that is, human factor VIII deficiency using autologous fibroblasts.[26]

[Chen et al, 12 *Gene Therapy* 655-667 (2005)(copy attached) at p. 664, col. 1 (emphasis added).] Reference 26 is the Roth et al. article. [Chen et al. at p. 667, col. 2.]

Thus, Applicant's invention has been recognized as pioneering, has been used by others with other genes and other cells, achieved a therapeutic effect in an animal model of a human disease, and achieved an actual therapeutic effect in humans. Other scientists have recognized this therapeutic effect in an animal model and in a human clinical trial. Moreover, none of the reasons the Examiner relies upon in the enablement rejection actually supports the rejection. Accordingly, it should be withdrawn.

<u>Indefiniteness Rejections</u>

The Examiner rejected the claims under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for various recitations in claims 72 and 104. Applicants have amended claims 72 and 104 to remove the language of concern, rendering this rejection moot.

CONCLUSION

For all the above-reasons, Applicant respectfully submits that the application is in condition for allowance. In light of the numerous times rejections withdrawn by a previous Examiner have been reasserted in this pre-GATT application, Applicant respectfully requests that the Examiner contact the undersigned with any remaining concerns she might have.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicants hereby request any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Date: January 27 , 2006

Respectfully submitted,
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